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EDITORIAL:

Another View of the Tamoxifen Trial

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The P-1 Tamoxifen Trial has claimed a benefit of nearly 50% reduction in the incidence of new breast cancers for those who took tamoxifen compared to placebo [1]. The implication is that breast cancer has been prevented and that we can generalize this benefit to a high-risk population of otherwise healthy women.

Almost 60,000 women volunteered to join the trial, believing that they were at high risk of developing breast cancer. Only 23% met the medical requirement of having at least a 2% risk of developing breast cancer over the next 5 years. The participants were randomized; half were given tamoxifen and the other half were given placebo. Although this was called a 5-year study, almost two-thirds had no 5-year follow-up and one-fourth did not have a 3-year follow up.

The desired benefit of less breast cancer in the tamoxifen group was found compared to the placebo group. There was a 48% decrease in breast cancer incidence in the tamoxifen group. Only a very small proportion of the participants actually developed breast cancer, making a 48% decrease in risk difficult to interpret.

Another way of looking at the result would be from a participant's point of view. Those participating in the placebo group had a 96.3% chance remaining healthy and not developing breast cancer during the study. Those in the tamoxifen group had a 98.1% chance of not developing breast cancer during the study. That gives those in the tamoxifen group a 1.8% benefit in avoiding breast cancer (Fig. 1). Since women who enter this study do not know whether they will actually develop breast cancer, the true benefit is a 1.8% improvement in their chance of avoiding breast cancer at 5 years.

This benefit included both invasive and noninvasive breast cancer, both above and below 50 years of age. The chance of avoiding invasive breast cancer for a woman entering the study improves from 97.3% in the placebo group to 98.6% in the tamoxifen group. The true benefit is 1.3% improvement in the chance of avoiding invasive breast cancer at 5 years (Fig. 2). In the over 50 years old group, the chance of avoiding invasive breast cancer increased from 97.4% to 98.7%, or a true benefit of 1.3% (Fig. 3).

Tamoxifen, like other estrogenic substances, affects uterine lining and coagulation status. These direct effects of increased estrogenic stimulation were monitored in both groups. A 140% increase in invasive uterine cancer was found in the tamoxifen group. Also, 58% more clinical strokes and 200% more pulmonary emboli were also seen in the tamoxifen group.

When prevention of disease in otherwise healthy women is considered, all tamoxifen-related benefits and morbidity should be examined. Adding the numbers of invasive breast cancers, invasive uterine cancers, pulmonary emboli, and strokes gives us a group of tamoxifen-associated benefits and health problems. Comparing the sum of these medical problems reveals that there are 220 pertinent medical problems in the placebo group compared to 181 in the tamoxifen group. This still favors the tamoxifen group, with an 18% overall reduction in these medical problems. However, a participant in the tamoxifen group increases her chances of remaining healthy and avoiding medical problems from 96.6 to 97.2%, an overall benefit of only 0.6% (Table I).

Examining the over 50 years old group of participants is clinically useful. These are the women dealing with the more imminent risk of breast cancer (due to age) and without many hormonal issues of the premenopausal patient taking tamoxifen. There is a significant decrease of invasive breast cancer in the women over 50 in the tamoxifen group. However, the tamoxifen group also has a significant increase in the incidence of uterine cancer, stroke, and pulmonary emboli. There is a 7% overall reduction in these medical problems in favor of the tamoxifen group over 50 years old (139 vs. 129 medical problems). A participant over 50 years old in the tamoxifen group increases her chance of remaining healthy and

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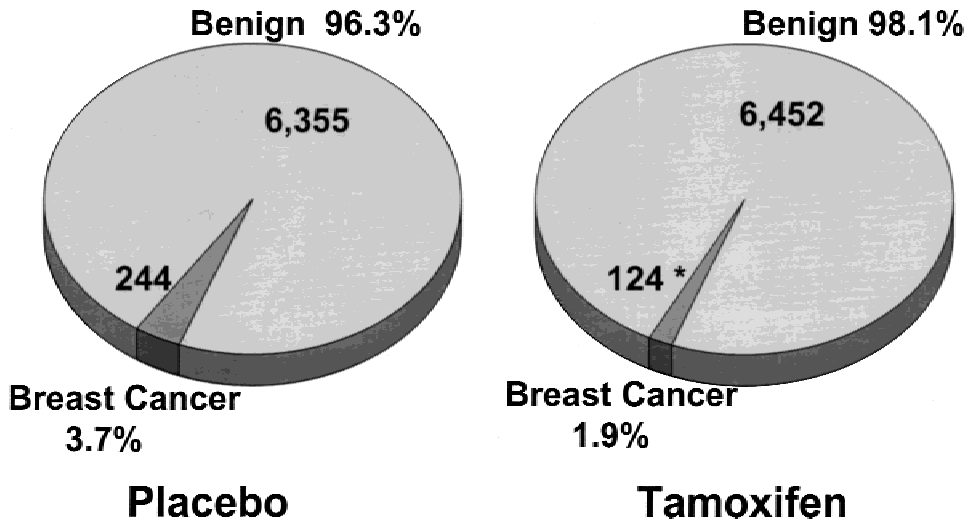

Fig. 1. Breast cancer in the total population of the tamoxifen prevention trial [1]. *$P < .00001$.

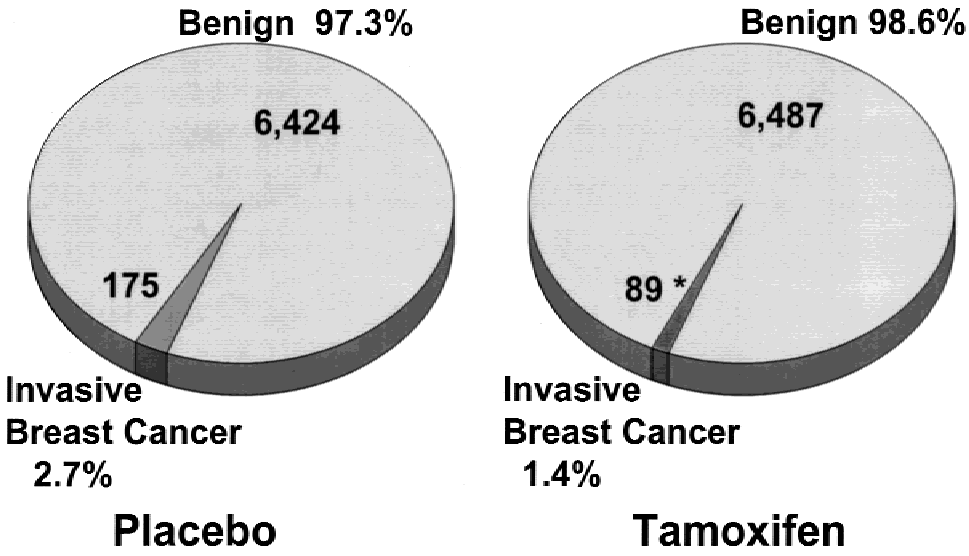

Fig. 2. Invasive breast cancer in the total population of the tamoxifen prevention trial [1]. *$P < .00001$.

avoiding medical problems from 96.6 to 96.9%, an overall benefit of only 0.3% (Fig. 4).

Ultimately, it is not morbidity that may be the most powerful measure of prevention benefit but mortality. There were fewer deaths due to breast cancer in the tamoxifen group than in the placebo group during the study (3 vs. 6). However, there was no overall significant difference in mortality. Causes of death, which may be influenced by tamoxifen, were increased. Death from breast cancer, uterine cancer, stroke, and pulmonary embolism are compared in the two groups. The same number of potentially tamoxifen-related deaths occurred in both groups (Fig. 5). There is not a tamoxifen-related mortality benefit in either group.

It is useful to compare the type of breast cancer in each group to further consider the potential mechanism of action. Size, nodal status, and estrogen receptor status were examined by comparing rates per 1,000 participants per year. Since there were twice as many breast cancers in the placebo group, measurement of rate per 1,000 participants per year may not be a fair standard for clinical comparison. We find it better to compare tumor characteristics of the cancers in each group.

The size of breast cancers found was similar in the two groups (Fig. 6). Of all the cancers that developed in both the placebo and tamoxifen groups, there were similar percentages of small and large breast cancers. Also, the proportions of node-positive and node-negative breast cancers were similar in the two groups (Fig. 7). This is not readily apparent when using rate comparisons. The

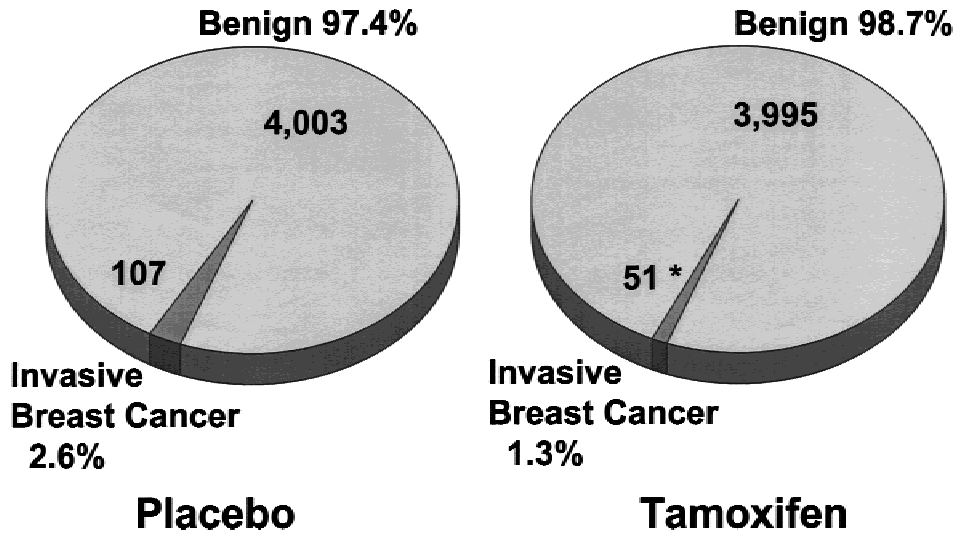

Fig. 3. Invasive breast cancer in the population over 50 years old in the tamoxifen prevention trial [1]. *$P < .05$.

TABLE I. No. of Tamoxifen-Related Medical Events in the Total Population of the Tamoxifen Prevention Trial [1]

	Placebo	Tamoxifen	% Change
Invasive cancer	175	89	−49
Endometrial cancer	15	36	+140
Stroke	24	38	+58
Pulmonary embolus	6	18	+200
Total no.	220	181	−18
Without events (%)	96.6	97.2	+0.6

claim that breast cancers in the tamoxifen group were smaller and less often node-positive is not supported when one compares the two groups this way.

The only difference in the measured breast cancer characteristics was the portion of estrogen-positive cancers that developed in each group. Three-fourths of the breast cancers in the placebo group were positive for estrogen receptor. Only half of the tamoxifen group were estrogen-positive. In contrast, both groups had equal numbers of estrogen receptor negative breast cancers (Fig. 8).

These findings show that the major difference between the breast cancer seen in the two groups is limited to the incidence of estrogen-positive tumors. This makes obvious sense recognizing the mechanism of tamoxifen and prior studies. Tamoxifen inhibits growth of estrogen-positive tumors [2–4]. As described by Fisher et al. [1], tamoxifen either prevents or delays . . . "the clinical expression of tumors." Considering the relatively short length of treatment by most of participants in this study, it is most likely that the effect of tamoxifen is to hinder the growth of preclinical existing estrogen-positive breast cancer. These small estrogen-positive tumors were inhibited from growth and likely kept in their preclinical phase. However, it is the estrogen-positive cancers that have a better prognosis and respond later to hormonal therapy.

Whether this suspension of growth would persist after tamoxifen was discontinued may not be known, since the trial was "completed." Participants in the placebo group may now take tamoxifen. One could argue that because of the premature closure of this trial and loss of a measurable control group, we may never know of any prolonged prevention benefit of tamoxifen in women without breast cancer. Lack of long-term follow-up of both groups will hamper clinical decisions when considering measures to influence lifetime risk.

In this study, there was no measurable impact on estrogen-negative tumors. It is the estrogen-negative tumor that is much more likely to develop systemic spread than the estrogen-positive tumor [5–8]. Since estrogen-negative tumors are often associated with worse prognostic factors, lack of any effect by tamoxifen on those tumors may limit any significant net mortality benefit.

Although an increase in endometrial cancer is found in the tamoxifen group, prior studies have implied that tamoxifen-induced endometrial cancer is a low-grade, early-stage cancer and should not be a cause of death in these patients [9]. A similar statement may be said of the type of breast cancer avoided by the use of tamoxifen. The characteristics of the breast cancer found by women taking placebo was <2 cm in 70%, estrogen positive in 75%, and with negative nodes in 65% [1]. Avoiding this type of tumor by the use of tamoxifen may not impact overall mortality.

Comparison of the P-1 prevention results with a recent study by Hartmann et al. [10] underscores the lack of substantial net prevention of morbidity and mortality. In that retrospective nonrandomized study, a group of high-risk patients underwent bilateral prophylactic mastec-

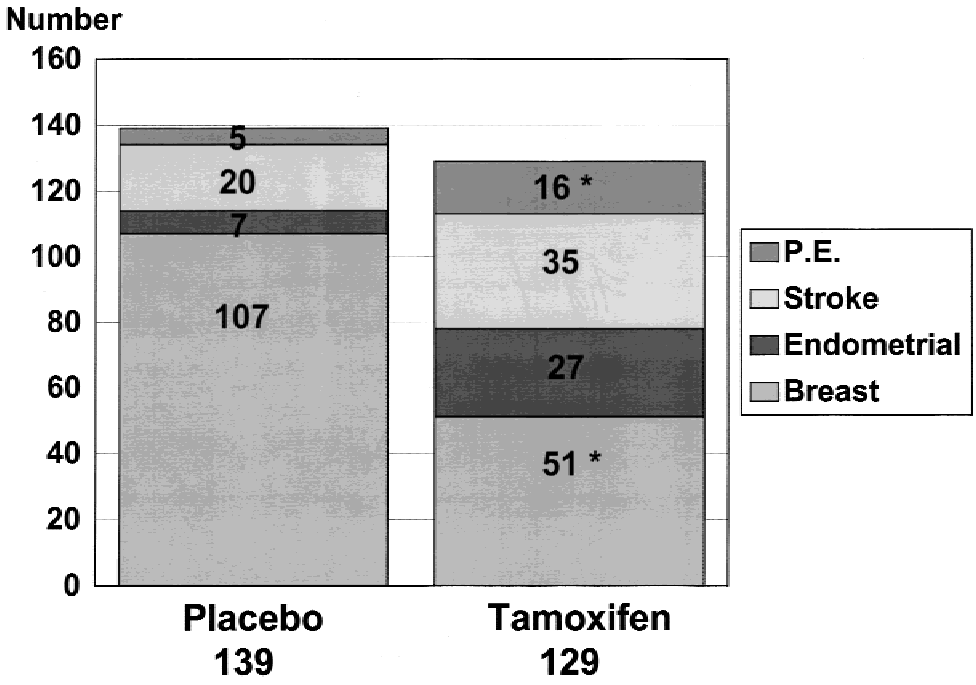

Fig. 4. Tamoxifen-related medical problems in the population over 50 years old in the tamoxifen prevention trial [1]. P.E. = pulmonary embolus, endometrial = invasive endometrial carcinoma, breast = invasive breast carcinoma. *$P < 0.05$.

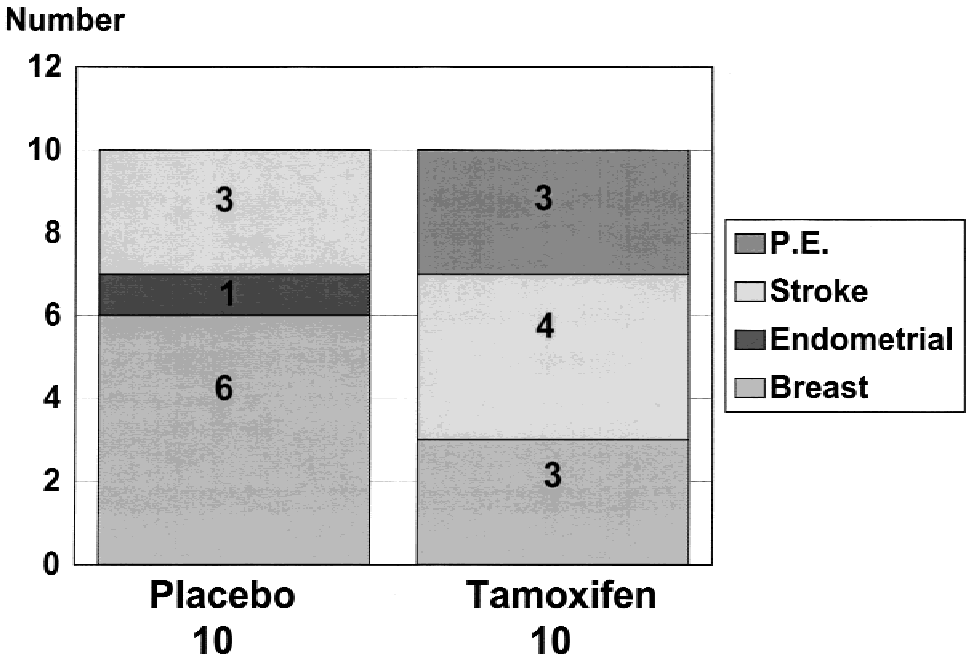

Fig. 5. Tamoxifen-related causes of death in the total population of the tamoxifen prevention trial [1]. P.E. = pulmonary embolus, endometrial = invasive endometrial carcinoma, breast = invasive breast carcinoma. *P* = not significant.

tomy and were followed for a mean period of 14 years. Results in those undergoing prophylactic surgery were compared with the subsequent development of breast cancer in their sisters who did not have preventive surgery. They were also compared to a Gail-model-calculated estimate of expected breast cancer incidence and mortality. Both morbidity and mortality were decreased between 80 and 90% in these high-risk women (Fig. 9). The long-term follow-up and the morbidity and mortality results from this surgical intervention make this study clinically useful.

At the time of counseling high-risk patients, the clini-

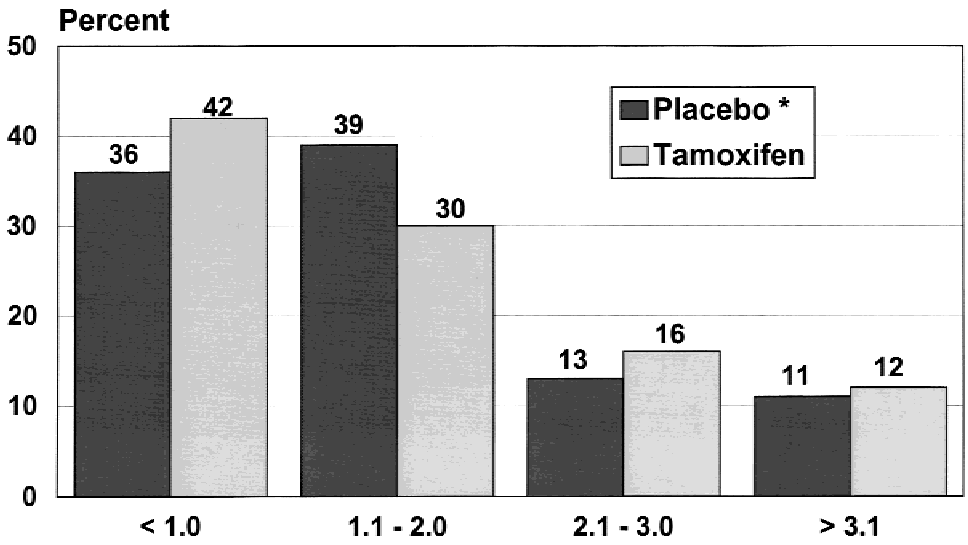

Fig. 6. Size of invasive breast cancer (cm) found in each group by percent [1]. *1% unknown size.

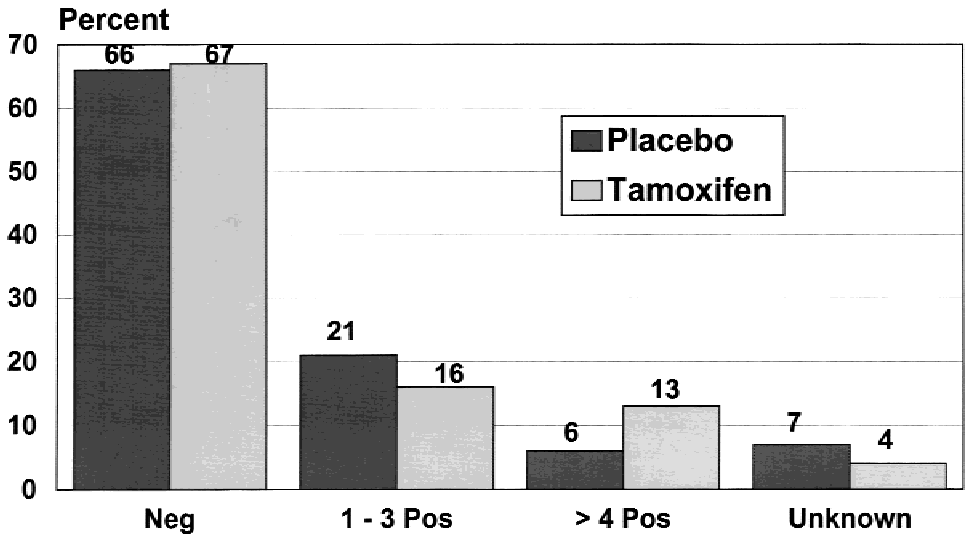

Fig. 7. Node status of invasive breast cancer found in each group by percent [1].

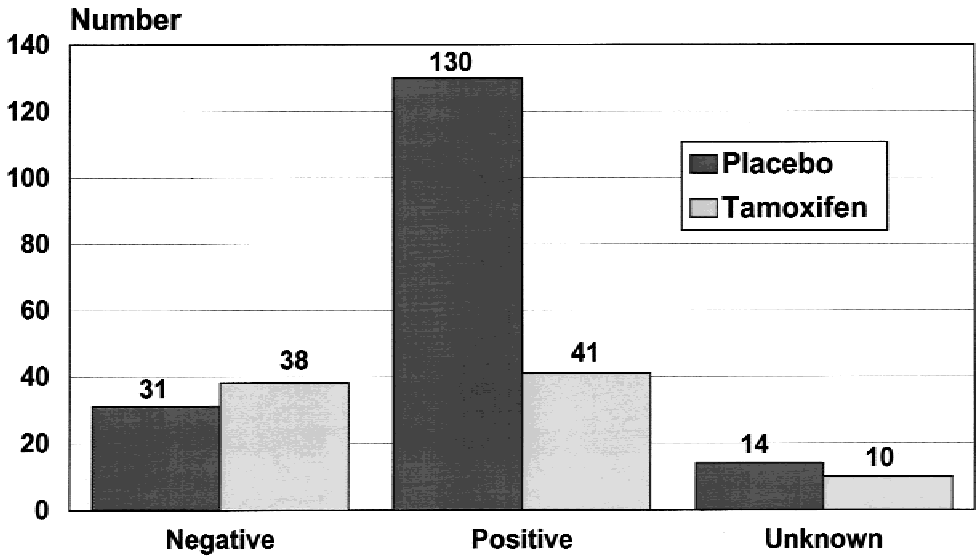

Fig. 8. Estrogen status of invasive breast cancer found in each group by number [1].

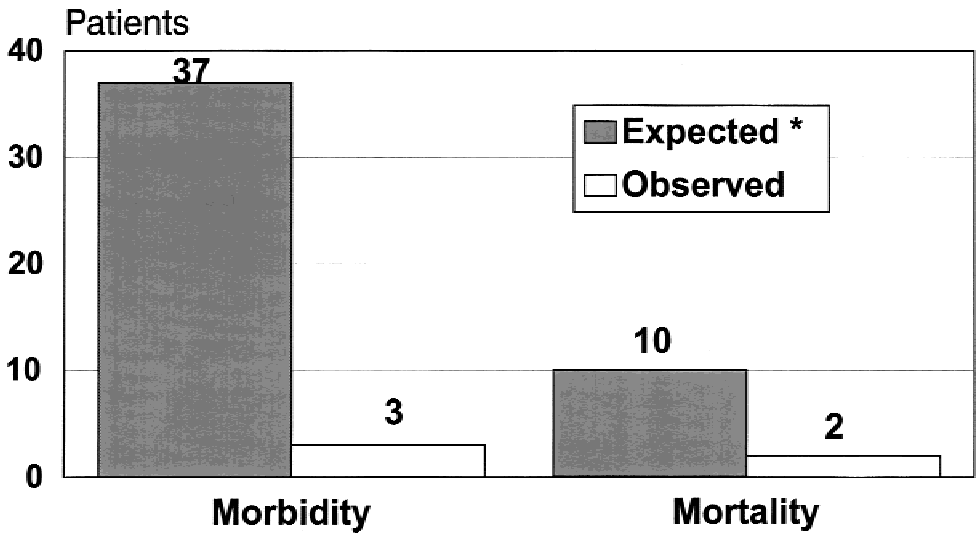

Fig. 9. Morbidity and mortality in high-risk women treated with bilateral prophylactic mastectomy ($n = 214$) [10]. *Gail model calculation (confirmed with cohort of sisters).

cian does not know which patient will actually develop breast cancer nor when it will occur. The only patient who truly benefits from breast cancer prevention is the patient who would otherwise develop breast cancer. Since most high-risk patients in the P-1 trial never would develop breast cancer, there is no benefit of prevention measures to the vast majority of such patients, yet they incur the risks of tamoxifen. They may not view improvement in the avoidance of breast cancer from 96 to 98% as a convincing benefit when examined with the morbidity and mortality data of this study.

When the goal of preventive measures is to preserve *overall* health in high-risk patients, the benefits of tamoxifen become marginal. Faced with tamoxifen prevention as an option, many women may choose other interventions that affect their risk of developing or dying from breast cancer (i.e., obtaining regular mammograms, exercise, avoiding obesity and alcohol).

As clinicians, we are confronted with the dilemma of managing patients at high-risk for breast cancer. As we counsel them, we must have realistic expectations of risks and benefits of preventive treatment [11]. Tamoxifen lessens the risk of breast cancer but new health risks are substituted. There appears to be no significant overall improvement in tamoxifen-influenced morbidity (+0.6%) and no effect on mortality.

Significant overall benefits will occur when we identify women at risk of breast cancer 10 to 20 times the risk for women in the current study. Then the net benefits should outweigh the risks. We should improve our methods of identifying women at the highest risk of developing breast cancer before the widespread use of tamoxifen as prevention becomes common.

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COMMENTARY

The "War on Cancer" waged over the last 3 decades has recently been criticized because too much emphasis has been placed on treatment and not enough on prevention [1]. It has been argued that much more could be

accomplished by altering behaviors that cause cancer or by other prevention strategies than by trying to find new treatments for established cancers. Obviously, both approaches deserve attention, but for most cancers we know little about their etiology or how to prevent them. This is especially true for breast cancer, although screening, a form of secondary prevention, has the potential of decreasing mortality. The recently published results of the National Surgical Adjuvant Breast Project's P-1 or Tamoxifen Chemoprevention Trial offer the potential for actually reducing breast cancer occurrence in high-risk women, something that has not been demonstrated previously [2]. Dr. Kaufman has carefully reanalyzed the data from this trial and offers another view of the results.

As Dr. Kaufman notes, the trial was initially intended to continue subjects on tamoxifen or placebo for 5 years, but follow-up was shorter than this in many patients. This was, in fact, partly the result of the scrutiny of the data monitoring committee, which periodically assessed the trial and mandated an early cessation and release of the results when the trial showed a strong statistically significant effect. While only a small number of study patients have developed cancer so far, the numbers of subjects in the trial and the risk levels of these women were chosen so as to give the statistical power to allow the conclusion that tamoxifen had a significant impact, if that were the case. By presenting the cancer incidence data in "reverse," as the chances of remaining healthy, Dr. Kaufman's analysis minimizes the impact of the results. This approach would be similar to presenting cancer treatment results as the percent increase in disease-free survival rather than the more usual percent decrease in recurrence. The former will almost always reduce the apparent magnitude of a treatment effect. It must be admitted, conversely, that the trend toward presenting clinical results as the percent reduction in relative risk of an event, rather than the absolute differences in survival or disease-free survival, does have the effect of magnifying the benefit of any intervention. Nevertheless, the percent reduction in the chances of an event, such as the diagnosis of breast cancer or the recurrence of a cancer in the adjuvant setting, provides a valuable point of reference for clinical decision-making and for discussing options with patients.

While the difference between 98.1% of patients remaining healthy on tamoxifen versus 96.3% with placebo may be a legitimate consideration from a public health point of view, individual women who face a high risk of developing breast cancer want to know what can reduce this risk and by how much. Although he reversed the numbers for breast cancer risk reduction to make them look smaller, Dr. Kaufman was more than happy to present the change in uterine cancer risk as a 140% increase and the risk of pulmonary emboli as a 200% increase, even though these events were very infrequent in this trial. He also ignored the strong trend indicating decreased osteoporosis and fractures in the total of "pertinent problems." Again, the total of medical problems may be an appropriate consideration for public health policy, but not all medical problems are created equal from women's points of view, and many women with risk factors for breast cancer are overwhelmingly concerned about that problem. The results of the P-1 trial offer some hope to these women and hope for further progress in the future. While mortality has not been decreased by tamoxifen at this early time, an overall survival benefit may be seen after longer follow-up. Dr. Kaufman could be correct in predicting that tamoxifen will have little impact on overall mortality, since most women don't die of breast cancer, but the long-term results of other trials (see below) argue otherwise.

Admittedly, the release of the results and allowing the women assigned to placebo to take tamoxifen if they chose eliminated our ability to assess some of the long-term differences between these two groups. However, once the results were known, the ethical considerations had to be balanced against the scientific issues. The women who courageously volunteered for this study were entitled to know the results and to act accordingly. The argument that tamoxifen may have treated subclinical cancers that were already present rather than preventing them is really semantic. Women who have tiny cancers that no one knows about and who never present with clinical disease because they took tamoxifen would still be spared the trauma of a cancer diagnosis and treatment. That may also be useful and worthwhile. However, the data from the B-14 trial refute the argument that tamoxifen "merely" treats small cancers rather than preventing them and also give us some information about what to expect from long-term outcomes after stopping tamoxifen. In B-14, women with node-negative, estrogen receptor (ER)–positive breast cancer were randomized to tamoxifen or placebo, and at 5 years, women taking tamoxifen were rerandomized to receive 5 more years of tamoxifen or placebo. In these women, tamoxifen produced long-term protection from recurrence and from contralateral breast cancers at 10 years, and there was no advantage to the additional 5 years of treatment [3]. All women taking tamoxifen had a statistically significant reduction in the incidence of cancers of the opposite breast at 10 years of follow-up. Similar data, which include the B-14 results and the results of other trials, come from the metaanalysis of tamoxifen trials, which showed a 47% reduction of contralateral breast cancer through 10 years for women receiving 5 years of tamoxifen [4]. These data indicate that tamoxifen likely does more than treat subclinical cancers, and that the benefit lasts long beyond the actual drug therapy. It is hoped that the same may be true for the P-1 subjects. Interestingly, the magnitude of the effect on contralateral cancers observed in B-14 was nearly identical to that seen in P-1. Moreover,

many of the cancers diagnosed in the P-1 trial were in situ lesions, which probably arose during the course of the trial.

Dr. Kaufman's reanalysis of the distribution of tumor sizes and node status is interesting but doesn't really alter interpretation of the results. In fact, it was not claimed, as suggested by Dr. Kaufman, that "breast cancers in the tamoxifen groups were smaller and less often node-positive." In fact, it was noted in the report of P-1 that "there was a decreased rate of invasive cancers that were ER positive, that were 2.0 cm or less in size, or that were associated with negative lymph nodes" [2]. In fact, there were very few tumors >2 cm in either group, and only one-third had positive nodes. The early-stage disease diagnosed in most patients is probably attributable more to the careful follow-up and screening of these patients than to the tamoxifen treatment. Certainly, it should not have been surprising, based on the mechanisms of tamoxifen action, that most of the decrease in breast cancer incidence was in the ER-positive group. However, while it is true that ER-negative tumors tend to be more aggressive, the implication that ER-positive tumors are not as worrisome or important as ER-negative tumors discounts the fact that many women die of metastases from ER-positive breast cancers every year. Decreasing the incidence of these tumors will certainly benefit those women, and we anxiously await an agent that has promise for prevention of hormone receptor negative cancers.

The comparison to prophylactic mastectomy certainly provides a standard against which to measure the tamoxifen effect, but this approach is far too extreme for most women such as those included in the P-1 trial, who did not have known or suspected mutations in the BRCA1 or BRCA2 genes. It will be interesting to learn, from future evaluations of the P-1 results along with genetic evaluation of the subjects, whether tamoxifen is effective for women with gene mutations. Since breast cancers associated with BRCA1 mutations are more likely to be ER-negative, these women may not benefit as much from tamoxifen and may still need to consider more extreme measures [5–7]. However, for other women, such as those with lobular carcinoma in situ or atypical ductal hyperplasia, whose risk for breast cancer is also very high, tamoxifen may offer real benefits, judging from the P-1 data. None of the alternative measures mentioned by Dr. Kaufman have similarly compelling data to support their ability to prevent or even inhibit breast cancer growth, and mammography only detects disease at early stages.

Admittedly, the published data from P-1 are early results, and ethical considerations did not allow us to continue the placebo group indefinitely, but these results are the first to demonstrate that any medical intervention can reduce the incidence of breast cancer. Even though Dr. Kaufman's alternative viewpoint may be correct insofar as it questions whether tamoxifen is the "final solution" to the breast cancer problem, tamoxifen does offer hope to many women who are highly motivated to do something to reduce their risk of developing this dreaded disease, which many of them have watched affect their mothers and siblings. It may not be time to prescribe tamoxifen for all women concerned about a high risk of breast cancer. For each of these women, the pros and cons of treatment and limitations of our knowledge must be carefully discussed before she decides whether or not to take tamoxifen, but many women will see the nearly 50% reduction in odds of developing breast cancer in the next 4–5 years as compelling, even if their risk is not overwhelming. Particularly in women under 50, who experienced very few of the most serious toxicities, such as endometrial cancer, the benefit probably outweighs the risks. Most importantly, the P-1 results offer hope that targeted, rationally designed prevention strategies for breast cancer can succeed. Perhaps with the study of tamoxifen and raloxifene for prevention of breast cancer, we can refine our approach. Even better ideas will undoubtedly be tested in the future.

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